

## **REMARKS**

Claims 26-33, 35 and 53-73 are currently pending in the application. Claims 26, 29, 31, 32, 35, 53, 57, 59, 63, 65, 66, and 67 are amended. Claim 74 is added. The amendments find support in the specification and are discussed in the relevant sections below. Support for newly added claim 74 is found in the claims and specification as originally filed, particularly Figure 13. No new matter is added.

### **Formal Matters**

#### **Objection to the Specification**

The Examiner objected to the specification because the abstract does not commence on a separate sheet in accordance with 37 C.F.R. §1.52(4)(b). Applicants have amended the specification to correct this defect.

The Examiner objected to the specification for containing hyperlinks to web addresses. The specification has been amended to delete the hyperlinks.

The Examiner objected to Table 1, noting that the title was obscured by a black patch. Applicants submit a new Table 1 herewith.

#### **Objections to the Drawings**

The Examiner has objected to Figures 2, 6, 7, 11, 12, and 14 for reasons of record. Applicants submit herewith new versions of Figures 2, 6, 7, 11, 12, and 14, which should obviate the Examiner's objections.

#### **Objection to the Claims**

The Examiner has objected to claims 26-33, 35, and 53-66 as being drawn to non-elected subject matter in the recitation of an inhibitor active on a gene encoding the polypeptide. Applicants have amended the claims to delete reference to this non-elected invention.

Accordingly, Applicants submit that each of the Examiner's objections has been addressed and remedied, and request reconsideration and withdrawal of the objections.

**Rejection of Claims 26-33, 35, and 53-66 Under 35 U.S.C. §112, First Paragraph**

The Examiner has rejected claims 26-33, 35, and 53-66 under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner asserts that while the specification is enabling for a method of inhibiting a bacterium by contacting the bacterium with “a specific inhibitor such as bacteriophage 77 ORF 104 peptide”, it is not enabling for a method of inhibiting a bacterium, or a method of treating or preventing a bacterial infection, where the structure of the inhibitor is not defined. Applicants respectfully disagree.

Applicants submit that the specification provides sufficient disclosure to enable one of skill in the art to make and use the claimed invention without undue experimentation. Applicant first wishes to point out to the Examiner that, as indicated at page 16, paragraph 2 of the Specification, the current invention lies in the disclosure of a novel protein of *Staphylococcus aureus*, namely DnaI, and uses thereof in screening, diagnostics and therapeutics. As mentioned throughout the specification, this new protein is involved in DNA replication and is, therefore, essential to *Staphylococcus aureus* growth and viability. The nucleotides and amino acid sequences of the *S. aureus* DnaI are provided. The specification further provides the nucleotide and amino acid sequences of a bacterial growth inhibitory bacteriophage polypeptide (77 ORF 104) which bind specifically and inhibit the activity of DnaI. The specification teaches still further, that the 77 ORF 104 specifically interacts with a minimal domain of DnaI comprising amino acids 150-313 of the *S. aureus* DnaI.

The Examiner's rejection hinges on the assertion that because the specification teaches a limited number of inhibitors useful for inhibiting the activity of DnaI, that the claims are not enabled for the methods as claimed. Applicants submit that the specification teaches how one of skill in the art would identify an inhibitor useful in the invention, and more importantly, how to determine whether an identified inhibitor is functional in inhibiting bacterial growth, or treating bacterial infection. Accordingly, one of skill in the art would be able to, following the teachings of the specification, obtain an additional inhibitor and use it according to the teachings of the specification to inhibit bacterial growth or treat/prevent bacterial infection. The Examiner, in contrast, contends that it would constitute undue experimentation for one of skill in the art to follow the teachings of the specification to identify additional inhibitors useful in the claimed

methods. The Examiner relies on the Wands factors to establish undue experimentation. Applicants' rebuttal to the Examiner's assertions for each of the factors is set out below.

*Breadth of the claims*

The Examiner asserts that the claims are broad and encompass unspecified variants regarding the inhibitor that acts on, binds to, or decreased the activity of DnaI. Applicants concur that the breadth of the claims encompass inhibitors inhibiting bacterial growth by binding to or by decreasing the activity of DnaI. The invention, however, does not rely solely on a specific type of compound that could be used to carry out the claimed method. Applicants' invention is based instead on the discovery of *S. aureus* DnaI activity as a useful pathway for bacterial growth inhibition. By identifying a new bacterial protein target for inhibiting bacterial growth, the present inventors have made a "pioneer" invention. Given the discovery of this novel protein, including its binding site, the art can now use this protein as a means for inhibiting bacterial growth, both *in vitro* and *in vivo*. Based on well settled law, the Applicants are entitled to broad claim scope commensurate with the magnitude of the scientific achievement advanced in the present application.

A considerable body of caselaw supports the principal that a patent claiming a pioneer invention is entitled to a broad scope. *E.g., Texas Instruments, Inc. v. United States Int'l Trade Comm'n*, 846 F.2d 1369, 1370 (Fed. Cir. 1988). Pioneer status "has to do with the position occupied by the invention in the art to which it pertains, or which it creates. . ." *MAC Corp. of America v. Williams Patent Crusher & Pulverizer Co.*, 767 F.2d 882, 884 n.3 (Fed. Cir. 1985). Generally speaking, a pioneer patent is "a patent covering a function never before performed, a wholly novel device, or one of such novelty and importance as to mark a distinct step in the progress of the art." *Westinghouse v. Boyden Power Brake Co.*, 170 U.S. 537, 561-62 (1898); *see also Texas Instruments*, 846 F.2d at 1370; *Breuer Elec. Mfg. Co. v. Tennant Co.*, 44 U.S.P.Q.2d 1259, 1267 (N.D. Ill. 1997) ("a pioneer patent is a distinct step in the progress of the art, distinguished from a mere improvement or perfection of what had gone before."). In contrasting a pioneer patent versus a patent which claims a mere improvement, the court in *Schneider (USA) Inc. v. Cordis Corp.* (29 U.S.P.Q.2d 1072, 1075 (D. Minn. 1993)) noted that "[a] pioneer invention is one which performs a function never performed by an earlier invention,

while an advance invention is one which performs a function previously performed by some earlier invention, but which performs that function in a substantially different way from any that proceeded it.” Applicants submit that the discovery of *S. aureus* DnaI and its interaction with 77 ORF 104, on which the present invention is based, is a wholly novel advance in the field of bacterial infection and its treatment, and should be accorded pioneer status. The present invention is based on the discovery of a critical biological pathway, essential to *S. aureus* infection, and which provides access to an effective means for killing the bacteria. Given that the DnaI pathway provides an accessible target for treating infections with critical phage proteins, it follows that the pathway would be likewise accessible to other inhibitors, a number of which have been described hereinabove.

As noted above, courts have adopted a liberal view of claim interpretations involving pioneering inventions. *Texas Instruments*, 846 F.2d at 1370 (citing to *Morley Sewing Machine Co. v. Lancaster*, 129 U.S. 263 (1889)). The general rule was stated by the Tenth Circuit: “a pioneer or primary patent...must be given a broad and liberal construction which should not be limited to the precise device and instrumentality shown.” *Swanson et al. v. Unarco Industries, Inc.* 178 U.S.P.Q. 17 (10th Cir. 1973). Further, *Studiengesellschaft Köhle v. Eastman Kodak Co.*, stated that “pioneering patents deserve broad protection, and we likewise note that a *patent need not list every imaginable permutation of its components or need it anticipate every possible modification developed by those who use it*” (emphasis added). 616 F.2d 1315, 1324, 206 USPQ 577, 600 (5<sup>th</sup> Cir. 1980).

Applicants submit that given the pioneer status of the present invention, coupled with the (1) disclosure of a specific inhibitor of *S. aureus* DnaI, (2) disclosure of methods for identifying and testing additional candidate inhibitors, and (3) the post-filing discoveries described below, using the methods taught in the specification, of additional growth inhibitors acting through DnaI, entitles Applicants to the full scope of the invention as claimed.

#### *Presence or absence of working examples*

The Examiner states that although the specification teaches that 77 ORF 104 inhibits bacterial growth, the specification does not provide any other working examples indicating the effects of other inhibitors. Indeed, Applicants have provided working examples detailing the

inhibition of bacterial growth according to the methods of the invention. The specification shows clearly that the bacteriophage 77 ORF 104 is a polypeptide which has a high killing potential when expressed in *S. aureus* (see Fig. 7, page 84, line 14 – page 85, line 2). Figures 12, 14 and 16 show clearly that the bacteriophage 77 ORF 104 polypeptide specifically binds to DnaI and fragments thereof. Figure 13 shows that, as expected, *S. aureus* DNA synthesis is inhibited by bacteriophage 77 ORF 104. Applicants note, however, that the law is clear that where the specification teaches one of skill in the art how to make and use the invention, no working examples are necessary (see, *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987); *In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970)).

In addition to the working example provided in the specification, the specification further provides teachings of how one of skill in the art would identify an inhibitor useful in the claimed methods. The specification teaches at pages 67-78, methods and assays which may be used to identify agents which act as inhibitors of DnaI and are thus useful according to the claimed invention. The specification teaches the types of agents which one of skill in the art would likely focus on to identify an inhibitor: small organic molecules, peptides, polypeptide, and antibodies (page 68). The specification teaches that such agents can, for example, be compounds related to and variants of 77 ORF 104. Applicants submit that, given the teaching in the specification that 77 ORF 104 is a specific inhibitor of DnaI, one of skill in the art would readily be able to identify variants and homologs of 77 ORF 104, and test them using the methods described in the specification (and referred to below) to determine whether such variants and homology function as inhibitors of DnaI. The specification teaches at page 70-75, binding-based assays to determine whether a candidate inhibitor binds to DnaI and therefore functions as a potential inhibitor of DnaI activity. Moreover, the specification teaches on pages 75-77, assays for determining whether a candidate inhibitor of the reduces the activity of DnaI. The specification further teaches at page 34 and 35, the definition of “decreases activity”, providing that a 10% decrease in activity of a candidate compound identifies that compound as an inhibitor. Thus, the specification teaches how to screen for an inhibitor of DnaI, and teaches further, criteria to be used in making a determination of whether a given compound is an inhibitor useful in the invention. Thus, in addition to the working example provided, the specification provides ample instruction to permit one of skill in the art to identify other inhibitors which may be used according to the invention without undue experimentation. In addition, the specification teaches

at pages 79-81, methods for administering an inhibitor to a cell or mammal, as well as dosage of an inhibitor according to the invention.

All of the techniques described in the specification which are employed to identify additional inhibitors of DnaI activity are well known in the art, and may readily be applied by one of skill in the art to identify additional inhibitors, based on Applicants' novel discovery of DnaI and its interaction with 77 ORF 104. In *In re Wands*, the court stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue' not 'experimentation'" (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The Court also stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (citing *In re Jackson*, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)).

As evidence of the routine experimentation required to identify additional inhibitors of DnaI, Applicants submit a Rule 132 Declaration which describes the identification of an additional inhibitor, PVLORF16, which displays *S. aureus* growth inhibitory activity. As described in the Rule 132 Declaration, based on the methodology taught in the present specification, Applicants were able to identify an additional phage protein binding specifically to *S. aureus* DnaI and inhibiting bacterial growth. Thus, Applicants submit that the specification provides sufficient teachings to permit one of skill in the art to identify bacterial growth inhibitory bacteriophages without undue experimentation.

The present invention also provides methods for identifying chemical compounds which bind to and inhibit the activity of DnaI (see more particularly pages 67 to 78). Furthermore, once in possession of a bacterial protein such as DnaI, it is well within the skill of those in the art to use known screening methods for identifying inhibitors of that particular bacterial protein and identify such inhibitors without undue experimentation. Indeed, using a screening method based on phage 77 ORF 104 and DnaI binding as disclosed in the present application (see, e.g., the FRET-based assay taught on page 73), the Applicants successfully identified chemical molecules

inhibiting bacterial growth via binding to DnaI and thus via inhibition of DNA replication. In that respect, the Examiner is respectfully requested to refer to the enclosed scientific paper (especially Table 1) which was recently published in Nature Biotechnology (Exhibit 1:Liu et al., Nature Biotechnology (2004) Vol. 22 pages 185-191), and which is authored by, among others, the three inventors of the present application. Liu et al. teach the identification of 11 small molecule compounds (out of 36 tested) which were capable of inhibiting growth of *S. aureus*. Two such compounds were selected for further testing and were determined to inhibit bacterial growth by inhibition of DnaI.

Accordingly, Applicants submit that the specification describes inhibitors useful in the claimed method, and teaches a specific example of an inhibitor which may be used according to the claimed method for inhibiting bacterial growth, and provides extensive teachings which would permit one of skill in the art to readily identify additional inhibitors useful in the invention. Applicants also submit, that they have identified, using the methods described in the specification, an additional example of a bacterial growth inhibitory bacteriophage polypeptide which inhibits bacterial growth via reduction in DnaI activity, and two small molecule compounds which inhibit bacterial growth via reduction of DnaI activity.

*State of the prior art and relative skill of those in the art*

The Examiner appears to suggest that the advanced state of the art with respect to treatment of *S. aureus* infection amounts to general knowledge that cannot be used to supplement omitted description in the specification. While Applicants agree with the legal argument that general knowledge in the art cannot be used to supplement omitted description in the specification, there is, in fact, no such omitted description in the instant case. The subject specification provides sufficient guidance to permit one of skill in the art to practice the invention without undue experimentation. As described above, the specification teaches how one of skill in the art would identify, in addition to the specific inhibitors taught, inhibitors of DnaI useful in the invention. The level of skill in the art with respect to the particular techniques and laboratory methods needed to carry out the identification of an inhibitor useful in the claimed methods is high. Thus, one of skill in the art could readily follow the teachings provided by the instant specification to conduct experiments to identify, in addition to those inhibitors

specifically taught, inhibitors which may be used in the claimed methods. Applicants respectfully remind the Examiner that the need for experimentation is not fatal to a finding of enablement, provided that the level of experiment required is not undue. Applicants submit that the specification provides sufficient guidance to preclude a finding of undue experimentation.

*Predictability or unpredictability of the art*

The Examiner asserts that the invention is unpredictable regarding the effects of various inhibitors in inhibiting bacterium, or in treating or preventing a bacterial infection in an animal. Applicants respectfully disagree. Applicants submit that the claims have been amended to recite that the inhibitor inhibits or reduces bacterial growth. Thus, one of skill in the art, based on the teachings in the specification would be able to determine additional (that is, in addition to the specific inhibitor taught) inhibitors which inhibit or reduce bacterial growth. Thus, the invention is not unpredictable regarding the effects of various inhibitors in inhibiting bacterium because the inhibitors for use in the invention are selected precisely based on their ability to inhibit bacterial growth. Applicants submit that it is well within the realm of reasonable experimentation for one of skill in the art to follow the teaching of the specification to identify inhibitors which have the recited effect on bacterial growth.

*The amount of direction or guidance and the quantity of experimentation necessary*

The Examiner asserts that the specification teaches 77ORF104 as an inhibitor of DnaI and *S. aureus*, but that the specification does not provide other working examples of other inhibitors, and does not provide sufficient teachings for the methods of treatment or prevention of bacterial infection, and is lacking in “guidance...to assess the effects of inhibitors in inhibiting bacterium or in the treatment of bacterial infection”.

Once again, the Applicants respectfully submit that the specification provides the teaching for identifying additional inhibitors. Although it may be necessary to carry out further experimentation to assess the effects of potential inhibitors against bacterial growth or in the course of the treatment of bacterial infection, these experiments are well within the realm of routine experimentation and do not require undue experimentation as evidenced by the data presented in the Rule 132 Declaration (attached) and in the Liu et al. reference. Moreover, as

described above, the specification provides ample teaching of dosage and administration parameters for the delivery of inhibitor compounds for the treatment or prevention of *S. aureus* infection. With respect to the Examiner's assertion that the specification does not teach how to assess the effects of inhibitors in inhibiting bacterium or in the treatment of bacterial infection, or how to monitor the effect of inhibitor in the prevention of infection, Applicants submit that such methods were routine in the art at the time of the filing of the subject application. It is well established that the specification need not disclose what is well known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463 (Fed. Cir. 1984). Applicants submit that assays for determining inhibition of bacterial growth, such as those taught in Example 1, were routine in the art at the time the application was filed. Likewise, as evidenced by the literature cited in the Background of the Invention, detection of *S. aureus* infection in humans was routine in the art. Thus, the specification does not need to provide redundant teachings as to how one of skill in the art would monitor the outcome of the claimed methods.

The specification provides ample guidance as to how to make and use the claimed invention, and provides further teachings as to how to identify and test for inhibitors of DnaI according to the invention. There is no undue experimentation required to assess the effects of inhibitors in inhibiting bacterium or in the treatment of bacterial infection, because the inhibitors are selected based on these criteria, and methods for monitoring such inhibition and/or treatment was routine in the art.

#### *Nature of the Invention*

The Examiner asserts that "the specification has not provided sufficient teachings on the treating conditions, nor has demonstrated the effects of inhibitors". As indicated hereinbefore, the claims now specify that the inhibitor inhibits bacterial growth. Figures 12 and 16 clearly demonstrate that *S. aureus* bacterial growth is inhibited and Figure 13 shows that growth inhibition occurs through inhibition of DnaI activity.

In summary, the Applicants submit that although the scope of the claim is broad, it is not overly broad. The specification provides a novel pathway by which bacterial infections can be prevented and/or treated. The specification also provides a new bacterial protein useful in the development of antibiotics as well as inhibitors binding to and reducing the activity of the bacterial protein thereby reducing bacterial growth. Identification of additional inhibitors using the teachings of the present application is within the skilled of those in the art and does not require undue experimentation as explained herein and as evidenced by the additional results presented in the Rule 132 Declaration accompanying this response, and in Liu et al.

**Rejection of Claims 26-33, 35, and 53-73 Under 35 U.S.C. §112, Second Paragraph**

The Examiner has rejected claims 26-33, 35, and 53-73 under 35 U.S.C. §112, second paragraph as being indefinite “because the claim lacks essential steps in the method of inhibiting a bacterium or treating a bacterial infection”. The Examiner asserts that claims 26-33, 35, and 53-73 omit an outcome step, and claims 26-30 and 53-64 omit an effective amount of inhibitor. Although not acquiescing to the rejection, Applicants have amended the claims to expedite prosecution. Specifically, Applicants have incorporated additional distinguishing characteristics into independent claims 26, 31, 35, 53, 59, 65, 66 and 67 to specify the outcome of the treatment (e.g. “inhibition of bacterial growth”, “thereby preventing said infection”), and to specify that the amount of inhibitor used is an “effective amount”. Independent claims 26, 53, 59 and 67 were also amended. Applicants accordingly request that the rejection be reconsidered and withdrawn.

The Examiner has rejected claims 29, 32, 57, and 63 as indefinite in the recitation of the term “a fragment or derivative or a bacteriophage inhibitor protein”. Applicants submit that the objected phrase “a fragment or derivative of a bacteriophage inhibitor protein” in claims 29, 32, 57 and 63 has been replaced by the term “bacterial growth inhibitory bacteriophage polypeptide”, which finds support throughout the specification, particularly page 85, lines 6-7, and page 38, lines 5-8. Applicants accordingly request that the rejection be reconsidered and withdrawn

**Conclusion**

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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